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Prediction of asparaginase-associated pancreatitis in children with acute lymphoblastic leukemia

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Asparaginase is a key drug in childhood acute lymphoblastic leukemia (ALL) therapy. Pancreatitis associated with asparaginase therapy (AAP) is a toxicity affecting 4–10% of children treated on contemporary ALL protocols and is associated with severe short and long term complications. It is important to understand what mechanisms predispose the patient to AAP. It is hypothesized that differences in sensitivity to asparaginase is caused by different clinical factors and host genome variants. A recent genome-wide association study has identified single nucleotide variants statistically significantly associated with AAP, but with insufficient odds ratios to allow clinical use [1]. In this study, we integrate information on risk groups, given treatment and genotypes of 1,390 childhood ALL patients (205 was diagnosed with pancreatitis) in the age of 1-17.9 into machine learning models to build robust classifiers of AAP at the time of diagnosis.

Feature selection of SNPs has been prioritized by three different strategies. One strategy is based on use of prior knowledge using SNPs annotated to genes that are known to be associated with risk of development of pancreatic disease; PRSS1, PRSS2, SPINK1, CTRC, CASR, CFTR, CPA1 and CLDN2 [2]. Other approaches included investigation of the predictive potential of results from [1] and by GTEx and by related gene interactions in pathways. The best performing model was a neural network with mean AUC: 0.68 with five-fold cross-validation. The model can provide insight towards clinical useful associations that possible can be applied for individual-level risk assessment for AAP.

References

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